14, 16, 18-20, 24, 26 and 28-30. The attached page is captioned "**Version with markings to show changes made**."

REMARKS

Claims 1-30 were originally filed with the present application, and are currently pending herein. All of the claims stand as rejected. Rejections of the claims are addressed separately below in the order raised in the outstanding Office Action, particularly in view of issues discussed during a telephone interview between Examiners Scheinberg and Marschel and Applicants' undersigned Attorney, on August 24, 2001. A summary of the interview is hereby provided, as requested by Examiner Scheinberg: The rejection of claims 8, 18 and 28 under §112, first paragraph was discussed. The Examiners reiterated and clarified that enabling the minimization step of the claims requires subtracting and multiplying like quantities; these quantities are defined in lines 6-10. Rejection of claims 4, 14 and 24, and claims 6, 16 and 26, were also discussed, and amendments to the claims for the purpose of overcoming the rejections were proposed and discussed. Finally, the rejection of claims 1, 11 and 21 under §102, teachings of the cited Ho reference, and possible means for overcoming the rejection, including amendments to claim 1, were addressed. Accordingly, entry of the above amendments, and reconsideration of the application, are respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 8, 18, and 28 are rejected under 35 U.S.C. § 112, first paragraph. As grounds for the rejection, the Office Action states on page 3 that "the operation of subtracting a vector . . . from the hot spot of a protein is not enabled; just as the operation of multiplication . . . is not enabled." Claim 8 is now amended to define H_j as "a position vector of a jth hot spot of the protein," and A_j as "a position vector of a jth atom of the at least one solution conformation." Applicants submit that it would have been clear to one of ordinary skill in the art that it would be necessary to express H_j and A_j as position vectors in order to successfully perform the arithmetic operations of the formula. However, the claims are amended as described above in order to state this explicitly. It is believed that the rejection is hereby overcome.

Claims 10, 20, and 30 are rejected under 35 USC §112, first paragraph, on the grounds that the BFGS optimization algorithm is not enabled by the disclosure. Applicants are required to amend the disclosure to include the material incorporated by reference. The specification is now so amended: formulae are incorporated explicitly, and what the variables represent in the context of the present invention is explained. As stated in the accompanying declaration executed by Applicants' undersigned Attorney, the amendatory material consists of the same material incorporated by reference. In support of the Declaration, a copy of the relevant pages of the reference is attached hereto. It is believed that the rejection is hereby overcome.

Rejections under 35 USC §112, Second Paragraph

Claims 4, 6, 8-10, 14, 16, 18-20, 24, 26 and 28-30 are rejected under 35 USC §112, second paragraph. The rejections are traversed.

Claims 4, 14, and 24 are rejected on the grounds that the term 'randomly' contradicts 'uniformly distributed'. In response to the rejection, each of these claims are now amended by deleting this term. The term refers to the uniform distribution containing all possible dihedral angles between two atoms, from which values are chosen in generating the conformations of the ligand. Applicants submit that one of ordinary skill in the art would understand that, in the claimed step of generating a plurality of conformation, values of dihedral angles between atoms in the conformation are chosen from all possible angles, 0° to 360°, since no subset of angles from which to chose is specified. (It is known in the art to limit the angles to defined values, for example, 60°, 270°, and 300°.) The term is deleted in order to clarify this meaning. It is believed that the rejection is hereby overcome.

Claims 8, 18, and 28 are rejected on the grounds that what the equation of the claims is 'minimizing' is unclear, and that clearly defined values are lacking in lines 6-10. Amendments to the claims addressing these issues are discussed above. It is believed that the rejection is hereby overcome.

Claims 6, 16, 26, 9, 19, 29, 10, 20, and 30 are rejected on the grounds that parameters that define a score in each of the claims is not provided. Claims 6, 16 and 26 are now amended to recite 'top clusters of hot spots' rather than 'clusters of hot spots with best scores'.

Support for the amendment may be found in the specificaiton on pages 14-15; for example, on page 15, lines 13-14, it is stated that, "for example, the top 30 clustered grid points may be retained". Claims 9, 19, and 29 are amended to specify that the atom pairwise score comprises "a hydrogen binding potential score or a steric potential score". Claims 10, 20 and 30 are amended to refer to the same score. Support for the amendments may be found on page 18, lines 12-13. Additionally, the scoring procedure of claims 9, 19, 29 and 10, 20, 30 is described on pages 17-20, with a detailed description of scoring parameters. It is believed that the rejection is hereby overcome.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-7, 9, 11-17, 19, 21-27 and 29 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ho *et al.*, (Pro. of 27th Hawaii Int'l Conf. on System Science, 1994). The rejection is traversed.
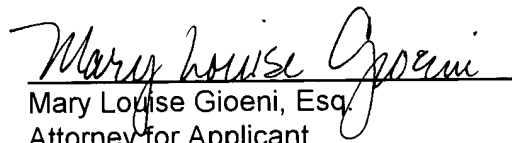
Ho *et al.* describe an automated system for facilitating drug design. The authors characterize such systems as being one of three types, *scanners*, *builders*, and *hybrids*. Database searching programs are in the *scanner* category, and the authors describe the scanner methodology as one wherein "recovered compounds" have "required binding elements in the correct orientation as specified by a query" (page 213, second paragraph). The method of the present invention belongs to the *scanner* category, since it utilizes a data base or library of compounds, and matches confirmations of those compounds to a binding site of a protein to yield ligands which complement the protein. *Builders* are defined as rational design programs which "spawn and evolve ligands from a seed structure within the active site" (page 213, third full paragraph). Ho *et al.*, state that their approach is a *hybrid*, which borrows techniques from both *scanners* and *builders*. They continue, "the active site of the target receptor is partitioned into subsites, each containing several pharmacophoric elements. Chemical fragments or 'building blocks' complimentary to each subsite are then retrieved from data bases. They are then linked to form composite ligands." (Page 213, last paragraph). *Hybrids* such as the method described by the reference, use <u>fragments</u> of chemical compounds in contrast to *scanners*, such as the method of the present invention, which use <u>entire</u> chemical compounds. Therefore, the procedure described by the reference differs

fundamentally from that of the claimed invention. Accordingly, claims 1, 11 and 21 are amended to recite, as suggested by Examiner Marschel during the telephone interview, that "said method does not involve assembly of two or more fragments to form the ligand." Support for the amendment may be found on page 5, lines 15-31, through page 6, lines 1-9, where the method of the present invention is distinguished from methods which initially dock fragments and build the ligand by attaching these fragments.

This fundamental difference may be seen particularly distinctly by comparing the first step of claim 1 with the corresponding step of the Ho procedure. Claim 1 recites as a first step "performing a pre-docking conformational search to generate multiple solution conformations of the ligand;" (lines 3-4, emphasis added). In contrast, Ho *et al.* perform a database search to generate molecular fragments. ("The core of our approach is the generation of molecular fragments" (page 216, second full paragraph, emphasis added).) The Office Action states on page 7 that the reference teaches "a three-dimensional data base search and retrieval program that uniquely generates and stores a set of multiple ligand solutions . . . . A search query of this data base generates preferred ligands that more effectively compliment the target receptor." With respect, Applicant submits that this is not an accurate characterization of the teachings of the reference. Rather, the approach of Ho is to generate molecular fragments which match binding sites on the protein, dock those fragments to the protein, edit the fragments, and assemble two or more fragments to form a ligand. This procedure would be impossible if it began with an assembled ligand. Furthermore, the authors state on page 214, second column, first paragraph, that their hybrid approach combines the strength of both scanning and building methods, while circumventing the disadvantages of each. These benefits could not be obtained if the scanner method were used. Therefore, because the reference does not teach the use of complete ligand structures throughout the procedures, Applicants submit that claims 1, 11 and 21 are not anticipated by the reference. Likewise, claims 2-7 and 9, which depend from claim 1, claims 12-17 and 19, which depend from claim 11, and claims 22-27, and 29, which depend from claim 21 are not anticipated by the reference. It is believed that the rejection is hereby overcome.

In view of the above amendments and remarks, Applicants respectfully request allowance of all claims pending herein.

Respectfully submitted,

Mary Louise Gioeni, Esq.
Attorney for Applicant
Reg. No. 41,779

Dated: September 17, 2001

HESLIN ROTHENBERG FARLEY & MESITI, P.C.
5 Columbia Circle
Albany, NY 12203-5160
Telephone: (518) 452-5600
Facsimile: (518) 452-5579

"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

In the Specification:

First paragraph on page 12 has been amended as follows:

(Amended) Referring to FIG. 3, uniformly distributed random conformations are generated allowing only rotatable bonds to vary 310. For example, 1,000 uniformly distributed random conformations can be generated varying only the rotatable bonds. The internal energy of each conformation is then minimized, again allowing only rotatable bonds to vary 320. Internal energy can be estimated, for example, using van der Waals potentials and dihedral angle term, reference: Diller, D.J. and C.L.M.J. Verlinde "A Critical Evaluation of Several Global Optimization Algorithms for the Purpose of Molecular Docking," Journal of Computational Chemistry, 1999, Vol. 20(16), p. 1740-1751, which is hereby incorporated herein by reference in its entirety. Each conformation can be minimized using, for example, a BFGS (Broyden-Fletcher-Goldfarb-Shanno) optimization algorithm[, e.g., reference Press, W.H., et al., Numerical Recipes in C, 2 ed., 1997, Cambridge: Cambridge University Press. 994, which is hereby incorporated herein by reference in its entirety]. **The algorithm is an updating formula used to iteratively build up an approximation of the minimum of a function *f*. The formula has the form:**

$$x_{i+1} = x_i - H_i \bullet \nabla f_i$$

$$H_{i+1} = H_i + \frac{\left(x_{i+1} - x_i\right) \otimes \left(x_{i+1} - x_i\right)}{\left(x_{i+1} - x_i\right) \cdot \left(\nabla f_{i+1} - \nabla f_i\right)} - \frac{\left[H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)\right] \otimes \left[H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)\right]}{\left(\nabla f_{i+1} - \nabla f_i\right) \cdot H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)} +$$

$$\left[\left(\nabla f_{i+1} - \nabla f_i\right) \cdot H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)\right] u \otimes u$$

where u is defined as the vector

$$u \equiv \frac{(x_{i+1} - x_i)}{(x_{i+1} - x_i) \cdot (\nabla f_{i+1} - \nabla f_i)} - \frac{H_i \cdot (\nabla f_{i+1} - \nabla f_i)}{(\nabla f_{i+1} - \nabla f_i) \cdot H_i \cdot (\nabla f_{i+1} - \nabla f_i)}$$

where

x_i is the vector of the initial position of the ligand;

x_{i+1} is the updated vector of the position of the ligand;

f_i is the function to be minimized, in this case, internal energy;

∇f_i is the gradient, or second derivative, of the function;

∇f_{i+1} is the updated gradient of the function;

H_i is the ith approximation to the inverse of the Hessian matrix (second derivatives of f);

and

$H_i + 1$ is the updated approximation to the inverse of the Hessian matrix.

The last paragraph on page 17, through line 3 on page 18, has been amended as follows:

(Amended) Each remaining match is optimized using [a] BFGS optimization algorithm as described above, wherein [with] a simple atom pairwise score is the function which is minimized 640. In one embodiment, the score can be modeled after the Piecewise Linear Potential (see, Gehlhaar, D.K., et al., "Molecular Recognition of The Inhibitor AG-1343 By HIV-1 Protease: Conformationally Flexible Docking by Evolutionary Programming," Chemistry & Biology, 1995, Vol. 2, p. 317-324, which is hereby incorporated herein by reference in its entirety) with a difference being that the score used herein is preferably differentiable. For this score, all hydrogens are ignored, and all non-hydrogen atoms are classified into one of four categories:

In the Claims:

Claims 1, 4, 6, 8, 9, 10, 11, 14, 16, 18, 19, 20, 21, 24, 26, 28, 29, 30 have been amended as follows:

(Amended)   1.   A method of docking a ligand to a protein comprising:

performing a pre-docking conformational search to generate multiple solution conformations of the ligand;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the ligand to obtain at least one ligand position relative to the protein in a ligand-protein complex formation; and

optimizing the at least one ligand position while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed;

wherein said method does not involve assembly of two or more fragments to form the ligand.

(Amended)   4.   The method of claim 1, wherein said performing the pre-docking conformational search comprises:

randomly generating a plurality of [uniformly distributed] conformations of the ligand;

minimizing a strain of each conformation of the plurality of [uniformly distributed] conformations;

using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

clustering the conformations and retaining a desired number of top clusters of conformations, said retained number of top clusters of conformations comprising said multiple solution conformations of the ligand.

(Amended)   6.   The method of claim 5, wherein said generating the binding site image further comprises:

placing a grid around the binding site of the protein;

determining a hot spot search volume using said grid;

determining hot spots using a grid-like search of the hot spot search volume;

and

for each type of hot spot, clustering the hot spots and retaining a desired number of top clusters of hot spots [with best scores], said desired number of top clusters comprising said multiple hot spots to be employed by said matching.

(Amended) 8. The method of claim 7, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

H_j = <u>a position vector of</u> a jth hot spot of the protein;

A_j = <u>a position vector of</u> a jth atom of the at least one solution conformation;

R = a 3×3 rotation matrix; and

T = a translation vector.

(Amended) 9. The method of claim 1, wherein said optimizing comprises optimizing multiple protein-ligand complex formations, said optimizing comprising:

eliminating each ligand position having a predetermined percentage of ligand atoms with a steric clash;

ranking remaining ligand positions using an atom pairwise score with a desired atom score cutoff, <u>said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score</u>;

after ranking, clustering the ligand positions and selecting a top number n of ligand positions; and

optimizing each ligand position of the n positions, allowing the translation, rotation and rotatable bonds of the ligand to vary.

(Amended) 10. The method of claim 9, wherein said optimizing comprises optimizing

each ligand position of the n positions using a <u>Broyden-Fletcher-Goldfarb-Shanno (BFGS)</u> [BFGS] optimization algorithm with <u>said</u> [a] simple atom pairwise score, allowing the translation, rotation and rotatable bonds of the ligand to vary.

(Amended) 11. A system for docking a ligand to a protein comprising:

means for performing a pre-docking conformational search to generate multiple solution conformations of the ligand;

means for generating a binding site image of the protein, said binding site image comprising multiple hot spots;

means for matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the ligand to obtain at least one ligand position relative to the protein; and

means for optimizing the at least one ligand position while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed<u>;</u>

<u>wherein said method does not involve assembly of two or more fragments to form the ligand</u>.

(Amended) 14. The system of claim 11, wherein said means for performing the pre-docking conformational search comprises:

means for randomly generating a plurality of [uniformly distributed] conformations of the ligand;

means for minimizing a strain of each conformation of the plurality of [uniformly distributed] conformations;

means for using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

means for clustering the conformations and retaining a desired number of top clusters of conformations, said retained number of top clusters of conformations comprising said multiple solution conformations of the ligand.

(Amended) 16. The system of claim 15, wherein said means for generating the binding site image further comprises:

means for placing a grid around the binding site of the protein;

means for determining a hot spot search volume using said grid;

means for determining hot spots using a grid-like search of the hot spot search volume; and

for each type of hot spot, means for clustering the hot spots and for retaining a desired number of <u>top</u> clusters of hot spots [with best scores], said desired number of <u>top</u> clusters comprising said multiple hot spots to be employed by said matching.

(Amended)   18.   The system of claim 17, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,\ T)\ =\ \sum_{j=1}^{3}\ \left| H_j\ -\ RA_j\ -\ T \right|^2$$

where:

<u>$I(R,T)$ = rms deviation between a jth hot spot and a jth atom of the at least one solution conformation;</u>

H_j =   position of a jth hot spot of the protein;

A_j =   position of a jth atom of the at least one solution conformation;

R =   a 3×3 rotation matrix; and

T =   a translation vector.

(Amended)   19.   The system of claim 11, wherein said means for optimizing comprises means for optimizing multiple protein-ligand complex formations, said means for optimizing comprising:

means for eliminating each ligand position having a predetermined percentage of ligand atoms with a steric clash;

means for ranking remaining ligand positions using an atom pairwise score with a desired atom score cutoff, <u>said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score</u>;

after ranking, means for clustering the ligand positions and selecting a top number n of ligand positions; and

means for optimizing each ligand position of the n positions, allowing the

translation, rotation and rotatable bonds of the ligand to vary.

(Amended) 20. The system of claim 19, wherein said means for optimizing comprises means for optimizing each ligand position of the n positions using a <u>Broyden-Fletcher-Goldfarb-Shanno (BFGS)</u> [BFGS] optimization algorithm with a simple atom pairwise score, allowing the translation, rotation and rotatable bonds of the ligand to vary.

(Amended) 21. At least one program storage device readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform a method of docking a ligand to a protein, comprising:

performing a pre-docking conformational search to generate multiple solution conformations of the ligand;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the ligand to obtain at least one ligand position relative to the protein; and

optimizing the at least one ligand position while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed <u>;</u> <u>wherein said method does not involve assembly of two or more fragments to form the ligand</u>.

(Amended) 24. The at least one program storage device of claim 21, wherein said performing the pre-docking conformational search comprises:

randomly generating a plurality of [uniformly distributed] conformations of the ligand;

minimizing a strain and a solvent accessible surface area of each conformation of the plurality of [uniformly distributed] conformations;

using the strain of each conformation to rank the conformations; and

clustering the conformations and retaining a desired number of top clusters of conformations, said retained number of top clusters of conformations comprising said multiple solution conformations of the ligand.

(Amended) 26. The at least one program storage device of claim 25, wherein said

generating the binding site image further comprises:

placing a grid around the binding site of the protein;

determining a hot spot search volume using said grid;

determining hot spots using a grid-like search of the hot spot search volume; and

for each type of hot spot, clustering the hot spots and retaining a desired number of <u>top</u> clusters of hot spots [with best scores], said desired number of <u>top</u> clusters comprising said multiple hot spots to be employed by said matching.

(Amended) 28. The at least one program storage device of claim 27, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R, T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

<u>$I(R,T)$ = rms deviation between a jth hot spot and a jth atom of the at least one solution conformation;</u>

H_j = <u>position of</u> a jth hot spot of the protein;

A_j = <u>position of</u> a jth atom of the at least one solution conformation;

R = a 3×3 rotation matrix; and

T = a translation vector.

(Amended) 29. The at least one program storage device of claim 21, wherein said optimizing comprises optimizing multiple protein-ligand complex formations, said optimizing comprising:

eliminating each ligand position having a predetermined percentage of ligand atoms with a steric clash;

ranking remaining ligand positions using an atom pairwise score with a desired

atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the ligand positions and selecting a top number n of ligand positions; and

optimizing each ligand position of the n positions, allowing the translation, rotation and rotatable bonds of the ligand to vary.

(Amended) 30. The at least one program storage device of claim 29, wherein said optimizing comprises optimizing each ligand position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) [BFGS] optimization algorithm with a simple atom pairwise score, allowing the translation, rotation and rotatable bonds of the ligand to vary.